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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

NGUYEN, QUANG

ART UNIT

PAPER NUMBER

1636

DATE MAILED: 04/23/2003

19

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/484,895

Applicant(s)

HARRINGTON ET AL.

Examiner

Quang Nguyen, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10/29/02, 10/30/02, 2/5/03.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 58,61-109 and 113-119 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 67-71,88,91,97,104,113,114,117 and 118 is/are allowed.
- 6) ☒ Claim(s) 58,61-65,72-74,76-82,84-87,89-90,92,95,96,98,99,101-103,105-109,115 and 116 is/are rejected.
- 7) ☒ Claim(s) 66,75,83,91,93,94,100,104 and 119 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). 19
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Applicants' amendments filed on 10/29/02 and 10/30/02 in Paper NOs. 14 and 15, respectively have been entered.

Amended claims 58, 61-109 and 113-119 are pending in the present application.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior Office Action.

Response to Amendment

The rejections in the previous Office Action are withdrawn in light of Applicants' amendment.

Following is a new ground of rejection.

Claim Rejections - 35 USC § 112

Claims 98-99 and 115-116 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 98-99 are drawn to a method for isolating eukaryotic cells *in vitro* in which a single exon gene has been activated, and a method for isolating a single exon gene cDNA using the vector of claim 97, respectively, and wherein the cells that express the first and second selectable marker sequences are selected.

Claims 115-116 are drawn to the vector of claim 70, wherein said negative selectable marker sequence is located upstream of said positive selectable marker, and the same wherein said vector further comprises one or more selectable marker sequence.

With respect to claims 98-99, the claims are not enabled because the vector of claim 97 to be utilized in the methods requiring the cells to express both the first and second selectable marker sequences, is not able to express the first selectable marker sequence upon the integration of the vector into a genome of a eukaryotic host cell as clearly recited in claim 97. Therefore, with the lack of sufficient guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the methods as claimed.

With respect to claims 115-116, the claims are not enabled because the vector construct of claim 70 specifically recites "wherein said splice donor site is 5' to said negative selectable marker and when said vector construct is integrated into the genome of a eukaryotic host cell and the vector-encoded splice donor is spliced to a splice acceptor in an endogenous gene in said genome, then said positive selectable marker sequence is expressed in active form and said negative marker sequence is not expressed", and under the limitation recited in claims 115 and 116 wherein the negative selectable marker sequence is located upstream of the positive selectable marker, then how is the positive selectable marker possibly expressed due to the splicing event between the vector-encoded splice donor and a splice acceptor in an endogenous gene in the genome (the positive selectable marker sequence is between the vector-encoded

splice donor and a splice acceptor in an endogenous gene in the genome upon integration of the vector into the genome of a cell)? The instant specification fails to provide sufficient guidance for a skilled artisan on how to make and use the vector as claimed. Furthermore, any essential or critical component that is needed to be present, and in which specific orientation in the vector, to yield the desired results must be recited. Otherwise, it would have required undue experimentation for a skilled artisan on how to make and use the vector as claimed.

Claims 101, 102-103, and 105-109 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

(1) A method for expressing a transcript containing exon I of an endogenous single exon gene, said method comprising: (a) transfecting one or more eukaryotic cells *in vitro* with the vector of any one of claims 58, 61, 65, or 67; (b) culturing said cells under conditions suitable for non-homologous integration of the vector into the genome of said cells; and (c) culturing said cells under conditions suitable for expression of a transcript containing exon I from an endogenous gene;

(2) A method for producing a gene product encoded by a genomic DNA or for isolating for a gene sequence as recited in claims 102 and 103, respectively, wherein said method comprises step (b) of inserting the vector of any one of claims 58, 61, 65 or 67 into the isolated genomic DNA, thereby producing a vector genomic-DNA complex;
or

(3) A method for producing a protein as recited in claim 106, wherein said method comprises step (b) of inserting the vector of any one of claims 58, 61, 65 or 67 into the isolated genomic DNA, thereby producing a vector genomic-DNA complex, and wherein the suitable host cell is a eukaryotic cell;

does not reasonably provide enablement for a method for expressing a transcript containing exon I of any gene; methods for producing a gene product encoded by a genomic DNA or for isolating a gene sequence or for producing a protein comprising a step of combining with the isolated genomic DNA, the vector of any one of claims 58, 61, 65 or 67 or the method of producing a protein of claim 106 in any suitable host cell in vitro. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 101 is drawn to a method for expressing a transcript containing exon I of a gene using the vector of any one of claims 58, 61, 65 or 67.

Claims 102-103, 105 and 108-109 are drawn to a method for producing a gene product encoded by a genomic DNA or for isolating a gene sequence by inserting into or otherwise combining with an isolating genomic DNA containing at least one gene from a eukaryotic cell the vector of any one of claims 58, 61, 65 or 67 to result in transcription of one or more nucleic acid sequences in a vector contained in a vector-genomic DNA complex.

Claims 106-107 are directed to a method for producing a protein comprising inserting into or otherwise combining with an isolated genomic DNA the vector of any

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one of claims 58, 61, 65 or 67 to produce a vector-genomic DNA complex for transfection into a suitable host cell *in vitro* to produce protein expression from said genomic DNA contained in the vector-genomic DNA complex.

The instant specification is not fully enabled for the presently claimed invention for the reasons discussed below.

(1) The breadth of the claims. With respect to claim 101, the claim encompasses a method for expressing a transcript containing exon I of any gene (e.g., a single exon gene or a multiple exons gene) using the vector of any one of claims 58, 61, 65 or 67 with the recited steps. With respect to claims 102-103 and 106-109, the claims encompass methods utilizing a step of inserting into or otherwise combining with an isolated genomic DNA the vector of any one of claims 58, 61, 65 or 67 to produce a vector-genomic DNA complex to generate a gene product or a protein encoded by said genomic DNA or for isolating a gene sequence. Additionally, the breadth of claims 106-107 encompasses a method for producing a protein in any suitable host cell (including non-eukaryotic cells) *in vitro*.

(2) The amount of direction or guidance provided by the specification. With respect to claim 101, the instant specification fails to provide sufficient guidance for a skilled artisan on how to make and use a transcript containing exon I of a multiple exons gene using the steps recited. It must be noted because of the presence of an unpaired splice donor site in the vectors of the present invention, exon I of an endogenous gene containing multiple exons is spliced out after the integration of the vectors into a genome of a eukaryotic cell. Then how can a transcript containing exon I of an

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endogenous gene containing multiple exons be obtained and used for any "real world" benefits by the method as claimed? In the absence of guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the method as claimed.

With respect to claims 102-103 and 106-109, apart from the teachings of inserting the vectors of the present invention into an isolated genomic DNA to produce a vector-genomic DNA complex for generating a gene product or a protein encoded by said genomic DNA or for isolating a gene sequence in a eukaryotic cell, the instant specification fails to provide sufficient guidance for a skilled artisan on how to combine the vectors of the present invention with the isolated genomic DNA in any manner without inserting (encompassed by the scope of combining) said vectors into said isolated genomic DNA to obtain the desired results. Without the insertion of the vectors into the genomic DNA, then how would a gene product or protein encoded by the genomic DNA be activated or driven by the promoters present in the vectors? The instant specification fails to provide any guidance for a skilled artisan on how to obtain a gene product or protein encoded by an isolated genomic DNA simply by combining said genomic DNA with the vectors of the present invention that does not necessarily require the insertion of the vectors into said genomic DNA. With the lack of sufficient guidance provided by the present disclosure, it would have required undue experimentation for a skilled artisan to make and use the methods as broadly claimed.

Additionally, with respect to claims 106-107 on the issue of any host cells encompassing non-eukaryotic cells such as prokaryotes or bacteria cells. Apart from

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the teachings of making and using the vectors of the presently claimed invention for non-targeted activation of endogenous genes in eukaryotic cells, the instant specification offers no guidance for a skilled artisan on how to make and use of the same in any non-eukaryotic cells. Moreover, it is well known in the art that unlike eukaryotes, in prokaryotes a polypeptide chain is generally encoded by a DNA sequence that is co-linear with the amino acid sequence (page 867, first paragraph, In Principles of Biochemistry (Lehninger et al., eds.), Second Edition, 1997; Cited previously) indicating that prokaryotes may not have the necessary components for mediating splicing of mRNA molecules. As such, then how would any of the vectors of the instant invention activate endogenous genes or genomic DNA contained in a vector genomic DNA complex for protein production in bacteria or prokaryotes? Therefore, with the lack of sufficient guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the instant broadly claimed invention.

Moreover, the physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

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Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 95 and 96 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 95 and 96, the term "said cDNA" is unclear. cDNA of step (e) or cDNA of step (f) in the method of claim 94? Which step do Applicants refer to? Clarification is requested because the metes and bounds of the claims are not clearly determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 58, 61-62, 65, 74, 77-79, 82, 84-87, 90, 92 and 102 are rejected under 35 U.S.C. 102(b) as being anticipated by Duyk et al. (Proc. Natl. Acad. Sci. U.S.A. 87:8995-8999, 1990; IDS).

Duyk et al. disclose the preparation of pETDV-SD that contains an exon 1 of the human β -globin (HBG) gene with an unpaired wild type HBG splice donor (SD) site at its 3' end that is operatively linked to the LTR promoter (see Fig. 1). The vector also contains an SV40 origin replication/early promoter operatively linked to aminoglycoside phosphoribosyl transferase gene from E.coli Tn5 (bacterial neo gene does not contain polyadenylation signal) that is in the same orientation as the LTR (see Fig. 1). Duyk et al. further teach the preparation of pETDV-SD: HBG(+) containing exon 2 of the HBG gene cloned into the *Bcl* I site of pETV-SD in the sense orientation, pETV-SD:RGReX.5 containing exon 5 of the rat glucocorticoid receptor gene into the *Bcl* I site of pETV-SD and a library of pETV:HLA1.5 plasmids containing a 1.527kb *Bst*YI fragment containing exons 4-6 of the HLA-A2 gene cloned into the *Bcl* I site of pETV-SD (see page 8995, under Plasmids). Duyk et al. also teach pETV-SD plasmids containing genomic DNA fragments cloned downstream from the exon trap are transfected into an ecotropic retroviral packaging cell line ψ -2, wherein the retroviral DNA is transcribed *in vivo* and transcripts derived from recombinant molecules that contain a functional splice acceptor (SA) site present in the cloned genomic DNA fragments may undergo a splicing event, and that both spliced and unspliced viral RNAs are packaged into virions (see page 8996, col. 2 under Experimental strategy).

Accordingly, the teachings of Duyk et al. meet the limitation of the instant claims, and therefore the claims are anticipated by the reference.

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Claims 58, 61-65, 73, 76, 78-79, 81, 84-87, 89 and 92 are rejected under 35 U.S.C. 102(e) as being anticipated by Treco et al. (U.S. Patent No. 6,270,989).

Treco et al. disclose the preparation of a targeting construct (pRTPO1) comprising in the following order a selectable marker *neo* gene (derived from the bacterial neomycin phosphotransferase gene that contains an endogenous promoter and without a polyadenylation signal), a mouse dihydrofolate reductase (*dhfr*) gene (an amplifiable marker gene), a regulatory sequence (e.g., CMV promoter) operatively linked to an exon flanked by an unpaired splice donor site at the 3' end of the exon, wherein the exon includes a CAP site and non-coding sequences or contains an ATG translation initiation codon in-frame with the coding sequences of the endogenous genes or encodes a sequence including portion of a signal peptide designed to improve cellular secretion, leader sequences, transmembrane domains and others (see Fig. 6 and cols. 10-14). Treco et al. further teach the DNA constructs to be introduced into cells to activate cellular endogenous genes under conditions suitable for homologous recombination (see col. 14).

Accordingly, the teachings of Treco et al. meet the limitations of the claims, and therefore the reference anticipates the instant claims.

Claims 58, 61-62, 65, 72, 78-80 and 84-86 are rejected under 35 U.S.C. 102(e) as being anticipated by Hay et al. (Proc. Natl. Acad. Sci. 94:5195-5200, 1997; IDS).

Hay et al. teaches the preparation of the vector pGMREP for P-element insertion-dependent gene activation in the *Drosophila* eye. The vector comprises in the following

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order: an *amp* gene (a bacterial gene that contains an endogenous promoter and without a polyadenylation signal), Glass binding site, hsp70 promoter, a fragment of glass genomic DNA containing the first exon 5' splice donor site (see Fig. 1, and page 5196, col. 1 underneath Fig. 1). Hay et al. further teaches the generation of transgenic flies containing pGMREP using standard procedures that require the transformation of flies embryos (see page 5196, col. 2).

Accordingly, the pGMREP vector containing P elements taught by Hay et al. meet every limitation of the vectors of the instant claims, and therefore the reference anticipates the instant claims.

Conclusions

Claims 67-71, 88, 91, 97, 104, 113-114 and 117-118 are allowable.

Claims 66, 75, 83, 91, 93-94, 100, 104 and 119 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, James Ketter, Ph.D., may be reached at (703) 308-1169, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Quang Nguyen, Ph.D.



JAMES KETTER
PRIMARY EXAMINER